115. Oxygenation of Dimethylsulfoxide and Copper-Catalyzed Autoxidation of Substituted Benzoins

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Summary

The catalytic activity of autoxidized copper(I) in the oxidation of *para*-disubstituted benzoins in dimethylsulfoxide by O_2 was studied both kinetically and by product analysis. Stoichiometry (*1*) accounts for more than 80% of the reaction. The catalytic oxidation was followed by monitoring the consumption of O_2 manometrically by a fully automatic apparatus.

$$X\text{–}C_6H_4\text{–}CH(OH)\text{–}CO\text{–}C_6H_4\text{–}X + O_2 + (CH_3)_2SO \xrightarrow{Cu^+ \text{ or } Cu_2O^{2+}} X\text{–}C_6H_4\text{–}CO\text{–}CO\text{–}C_6H_4\text{–}X + (CH_3)_2SO_2 + H_2O \quad (1)$$

(X = H, CH_3, OCH_3, C_6H_5, Cl)

A redox shuttle mechanism is proposed, where the rate-determining step is the autoxidation of Cu(I) followed by a rapid oxidation of the substrate by an oxocupric species. The redox stoichiometry (*1*) corresponds to that found for external monooxygenases (or mixed-function oxidases), and the significance of our results with respect to analogous catalytic systems is discussed.

Introduction. – Copper complexes are important catalysts for the oxidation and oxygenation of organic substrates by molecular oxygen both in low-molecular and in biological systems [1] [2]. Catalytic oxidation (or, more specifically, dehydrogenation) can frequently be achieved by simple copper salts in aqueous solution. Well-known examples of that type are the oxidation of ascorbic acid to dehydroascorbate [2–4], of aromatic amines [5], or of thiols [6] [7]. On the other hand, with very few exceptions [8], oxygenation, *i.e.* direct incorporation of one or both atoms of O_2 into the organic substrate needs strongly basic and aprotic conditions at least for non-enzymatic reactions.

Probably the best studied of these systems is obtained from autoxidized CuCl in pyridine with various co-solvents [9]. This type of reagent is equally active in the oxidative coupling of phenols [10] [11], in the oxidative ring cleavage in catechols or *o*-quinones [12] [13], in the oxygenation of phenols [9] [13], and in the oxidation of benzoin

to benzoic acid [14] [15]. Many details of these reactions are still unknown and so far there is only weak evidence for actual catalytic oxygenation. The oxidative cleavage of catechols is apparently effected by an oxocupric species, and O_2 is only needed for re-oxidation of Cu(I) [9]. Oxygenation of phenols needs Cu(I) and O_2, but has not yet been made catalytic in this system [13].

An interesting phenol oxygenation in a binuclear Cu(I)-complex has been discussed as a model for copper-containing monooxygenases such as tyrosinase and dopamine-β-hydroxylase [16]. While there is hope that this very clean reaction will give detailed insight into the mechanism of oxygenation, it needs stoichiometric amounts of metal ion, and it is presently unclear whether a truly catalytic system may be obtained on that basis [17].

Some time ago we have reported that a rather versatile catalyst may be obtained from the autoxidation of Cu(I) in dimethylsulfoxide (DMSO) [18] [19]. This system is truly catalytic, and the oxidation of various substrates such as 2,6-dimethylphenol to poly(2,6-dimethyl-1,4-phenylene ether), 3,5-di(*t*-butyl)catechol to 3,5-di(*t*-butyl)-*o*-benzoquinone, and benzoin to benzil is intimately coupled to the oxygenation of DMSO to $(CH_3)_2SO_2$. The overall stoichiometry is given by *Eqn. 2* and is identical with that of external monooxygenases. The catalytic cycle can be separated into two main steps, the oxygenation of DMSO to $(CH_3)_2SO_2$ concomitant with the autoxidation of Cu^+ *(Eqn. 3)*, and a rapid regeneration of Cu^+ by the organic reductant SH_2 *(Eqn. 4)*.

$$SH_2 + O_2 + (CH_3)_2SO \xrightarrow{Cu^+ \text{ or } Cu_2O^{2+}} S + H_2O + (CH_3)_2SO_2 \quad (2)$$

$$2\ Cu^+ + O_2 + (CH_3)_2SO \longrightarrow Cu_2O^{2+} + (CH_3)_2SO_2 \quad (3)$$

$$Cu_2O^{2+} + SH_2 \longrightarrow 2\ Cu^+ + S + H_2O \quad (4)$$

In the present study, the oxidation of several benzoins **1**–**5** to the corresponding benzils **1a**–**5a** is described. Steric contributions were minimized by the exclusive use of *para*-disubstituted derivatives.

$$X\text{–}C_6H_4\text{–}CH(OH)\text{–}CO\text{–}C_6H_4\text{–}X$$

1: X = H; **2**: X = CH_3; **3**: X = OCH_3; **4**: X = Cl; **5**: X = C_6H_5

Experimental. – *Materials.* Benzoin *(Fluka, purum)* was recrystallized from EtOH, m.p. 406–407 K ([20]: 405.5–406.5 K). The *para*-disubstituted benzoins **2**–**5** were synthesized according to standard literature procedures and were characterized by m.p. and IR spectra. **2**: m.p. 360–361 K ([21]: 361–362 K); **3**: m.p. 383–384 K ([22]: 386 K); **4**: m.p. 360 K ([23]: 360–361 K); **5**: m.p. 440–442 K ([24]: 441–443 K). $[Cu(CH_3CN)_4]BF_4$ was synthesized according to [25] and used as a 0.25M solution in CH_3CN. DMSO *(Merck, uvasol)* was distilled over CaH_2 under reduced pressure of N_2. $(CH_3)_2S$ (*Merck*, zur Synthese) was distilled under N_2. $(CH_3)_2SO_2$ (*Merck*, zur Synthese) and all other reagents, which were of *p.a.* grade, were used without further purification.

Measurements and Product Analysis. The consumption of O_2 as a function of time was measured with a microprocessor-controlled automatic gas volumeter [26] under atmospheric pressure of pure O_2 at 298 K. 0.01–0.2 mmol of $[Cu(CH_3CN)_4]BF_4$ in CH_3CN were added to 1 mmol of the respective benzoin dissolved in 10 ml of DMSO.

At the end of the kinetic runs, the catalyst was destroyed by adding aq. HCl to the reaction mixture, and the products were extracted with $CHCl_3$. The org. phase was washed with H_2O, dried (Na_2SO_4) and evaporated. The benzils were recrystallized and characterized by m.p., IR, and ^{1}H-NMR spectroscopy. **1a**: m.p. 367.5–368 K ([27]: 368 K); **2a**: m.p. 376–376.5 K ([21]: 377–378 K); **3a**: m.p. 404–405 K ([22]: 406 K); **4a**: m.p. 472–473 K ([28]: 473 K); **5a**: m.p. 413–414 K ([24]: 414–415 K). $(CH_3)_2SO_2$ was quantitatively determined by gas chromatography (GC) using a *Perkin Elmer 3920* with 3% *Carbowax* on *Chromosorb* as stationary phase (t_R at 413 K: DMSO 1.9 min, $(CH_3)_2SO_2$ 3.1 min). With **1** (X = H) and **3** (X = OCH_3), benzoic acid (*Varian 1400, Chromosorb 101*, t_R 13 min at 503 K) and *p*-methoxybenzaldehyde (conditions as with $(CH_3)_2SO_2$, t_R 4.0 min), respectively, were found in yields of less than 1%.

p-Methoxybenzaldehyde was identified by GC-MS (*MAT 212/SS188*, $M^+ = 136$). $(CH_3)_2S$ (GC *Perkin Elmer F11* using 5% FFAP on *Chromosorb*, t_R 2.1 min at 316 K) could not be found in any reaction solution.

Results and Discussion. – The substituted benzoins are catalytically oxidized into the corresponding benzils. No oxidation is observed with simple cupric salts or with Cu(I) in acidic solution, even if stoichiometric amounts of metal ion are used. As shown in the *Table*, yields of the crude benzils were essentially quantitative. With the

Table. *Results of Product Analysis and O_2-Uptake*[a])

X	O_2 [%][b])	$(CH_3)_2SO_2$ [%][b])	Benzil [%][b])		v_0[c])	Catal. cycles
H	78	67	99[d])	88[e])[f])	0.087	80
CH_3	58[g])	56[g])	93[d])	85[e])	0.083	150
OCH_3	70	60	94[d])	86[e])	0.115	80
C_6H_5	62	59	92[d])	86[e])	0.098	80
Cl[h])	44	54	103[d])	61[e])	0.068	25

[a]) 0.05 mmol Cu(I) added to 1 mmol of substrate. [b]) Based on stoichiometry (*1*). Initial rate of O_2-uptake in mmol/min. [d]) Crude product. [e]) Yield after recrystallization. [f]) After special workup of all mother liquors, 95% of **1** were obtained. [g]) 0.075 mmol of Cu(I) used. [h]) Heterogenous system with precipitation of benzil.

exception of the chloro compound, more than 85% could easily be obtained in pure form after recrystallization. Only traces of benzoic acid (X = H) and *p*-methoxybenzaldehyde (X = OCH_3) were found as by-products by gas chromatography. With all benzoins some reaction inactivation is observed. This is most important at low catalyst ratios, where a large number of catalytic cycles is needed for complete substrate oxidation. Likely this is due to protonation of the Cu_2O^{2+} species, leading to inactive Cu(II). All reactions are truly catalytic, however. As indicated in the *Table*, between 25 (**4**) and 150 (**3**) catalytic cycles can be obtained with the different substrates. The dichloro benzoin **4** is the most acidic among the substrates studied and has the largest ability to deactivate the catalyst. In addition, the dichloro compound forms a heterogenous system after the early stages of the reaction, which also may lead to incomplete oxidation through co-precipitation. Except for **4**, conversion of the benzoins into the benzils is essentially quantitative for a copper-to-substrate ratio of 0.05.

For substrates **1**–**3** and **5** 0.6–0.8 mol of O_2 per mol of benzoin are consumed. DMSO serves as a co-substrate and is oxygenated during the reaction. Up to 0.8 equiv. of $(CH_3)_2SO_2$ are produced. In line with the incomplete formation of the benzil **4a**, the amount of O_2 consumed (0.44 equiv.) is significantly reduced for the dichloro compound. For substrates **1** (X = H) and **3** (X = OCH_3) the dependence of O_2 consumed

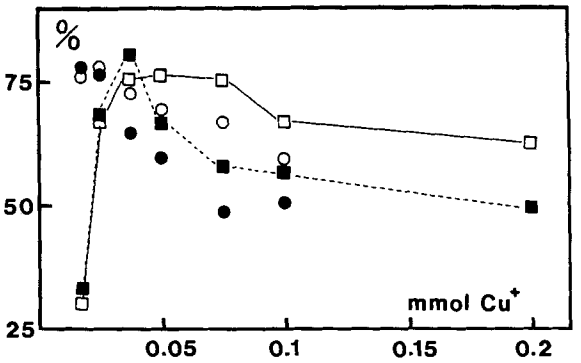

Fig. 1. *Percentage, based on stoichiometry (1), of O_2 consumed* (open symbols) *and of $(CH_3)_2SO_2$ formed* (full symbols) *for benzoin* (□) *and dimethoxybenzoin* (○) *as a function of the catalyst concentration*

and of sulfone formed was studied as a function of the catalyst concentration, as indicated in *Fig. 1*. For very small concentrations, the reaction is incomplete due to reaction inactivation. The amounts of O_2 used and of sulfone formed have a maximum with a catalyst ratio of 2% for **3** and 4% for **1**, respectively. This is explained by assuming two different stoichiometries (*2*) and (*5*). *Eqn. 2* prevails at low catalyst concentrations, where equimolar amounts of O_2 are consumed and of sulfone are formed.

$$SH_2 + \tfrac{1}{2}\, O_2 \xrightarrow{Cu^+ \text{ or } Cu_2O^{2+}} S + H_2O \qquad (5)$$

It is partially obscured by the concomitant deactivation of Cu_2O^{2+} for very low copper-to-substrate ratios. Stoichiometry (*5*) prevails at higher copper concentrations. It uses only one half O_2 per benzoin and does not lead to the formation of $(CH_3)_2SO_2$. From *Fig. 1* we conclude that stoichiometry (*5*) accounts for almost 50% of the total reaction at the highest catalyst ratio. Oxidation of the benzoins to the corresponding benzils remains essentially quantitative at the higher catalyst concentrations.

Reaction inactivation is least important with the methoxy derivative **3**. This is probably due to the electron-donating properties of the *p*-methoxy group which makes the benzoin less acidic and leads to decreasing protonation of Cu_2O^{2+} and thus to reduced inactivation. In line with this, *p*-CH_3O–C_6H_4COOH is the least acidic of the corresponding benzoic acids [29] (*cf.* also *Fig. 3*).

In *Fig. 2* the initial rates of O_2-consumption are plotted as a function of the catalyst concentration for the five substrates. The rates are obviously not identical, but with the exception of the chloro compound **4** for the lowest amount of copper they are reasonably close, *i.e.* they differ by a factor of two or less. This is quite in line with the ideas developed on the basis of our earlier experiments with the parent compound **1** [19] suggesting a ping-pong mechanism (*3*), (*4*) with Cu(I)-autoxidation as the rate-limiting step. Some minor effect of the substrate on the autoxidation of Cu(I) has been observed in these previous experiments, too. The upper limiting rate of O_2-uptake, roughly 0.12 mmol·min^{-1}, which seems to be common to all substrates but **4** is somewhat surprising and not really explained so far. The limiting rate of the apparatus is

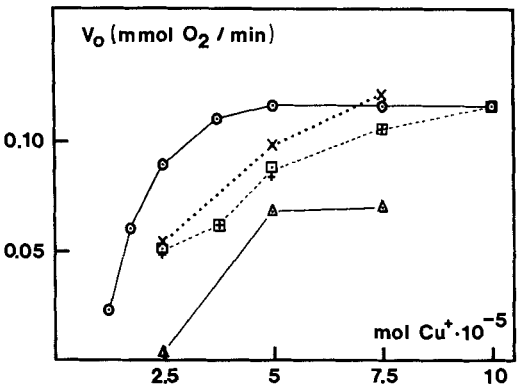

Fig. 2. *Initial rates of O_2-consumption as a function of catalyst concentration.* Unsubstituted benzoin: □; dimethylbenzoin: +, ----; dimethoxybenzoin: ○, ———; diphenylbenzoin: X, · · · · ·; dichlorobenzoin: △, ———.

higher by more than a factor of two [26]. This problem has not been studied any further, but a mechanism in which the rate of O_2-uptake is independent of the concentration of the catalyst would be difficult to imagine and perhaps it is more likely that the properties of the DMSO solution are modified by the substrates to obtain a slower diffusion of O_2 into the solvent.

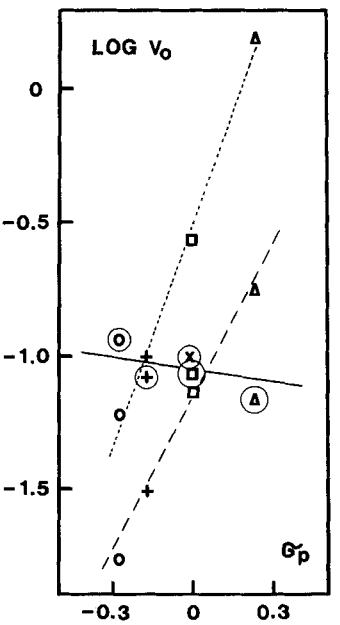

Fig. 3. Hammett *plot for catalytic oxidations of substituted benzoins. a)* Copper catalysis in DMSO, this work (———); *b)* base catalysis in H_2O [29] (· · · · ·); *c)* catalysis by nickel acetate in MeOH [33] (– – – –). Symbols for the substrates as in *Fig. 2.*

In many copper-catalyzed oxidations [2] [3] [8] [30] of organic compounds, deprotonation of the substrate is an essential and sometimes rate-limiting [31] [32] step. Quite in contrast, increasing acidity of the substrates decreases rather than increases the rate of oxidation in our system. A *Hammett* plot is shown in *Fig. 3*, curve *a*, together with results from the base-catalyzed autoxidation of benzoins in water [29] (curve *b*), and from their oxidation in MeOH catalyzed by nickel acetate [30] (curve *c*). A strong positive correlation is observed in curves *b* and *c*, and these systems require a mechanism where deprotonation of the substrates is the rate-determining step. The opposite dependence is indicated for our system in curve *a*, but *Fig. 3* clearly shows that here the influence of the substituents and thus of the basicity of the benzoins is less important.

To summarize, Cu(I) in DMSO provides an effective catalyst for the oxidation of substituted benzoins by O_2. The reaction is strongly, although not completely, coupled to the oxygenation of DMSO to $(CH_3)_2SO_2$, providing a so far unique low-molecular system with the stoichiometry of external monooxygenases (*1*). The catalytic factor could not be determined, but must be several orders of magnitude, since no O_2-uptake could be measured in the absence of metal ion.

Relative to other catalytic oxidations of substituted benzoins the nature of X in **1–5** is not extremely important. The observed effects, are, however, well in line with our ideas about the catalytic process which depends on the integrity of a strongly basic oxocupric species Cu_2O^{2+} as the active oxidant. The most electron-donating group CH_3O (**3**) gives the highest initial rates and the highest number of catalytic cycles, it is least susceptible to reaction inactivation. The converse is true for the most acidic of the substrates, **4**.

It is worth noting that our system and monooxygenases may have more features in common than the mere stoichiometry (*1*). According to the present ideas oxygenation of phenols in tyrosinase is accomplished by a binuclear μ-peroxo complex $Cu_2O_2^{2+}$. The catechol thus produced is then oxidized by a dimeric Cu(II)-complex, probably bridged by a RO^--group from a tyrosine residue [2] [34]. Exactly the same seems to be true in our system, where oxygenation of DMSO is coupled to the autoxidation of Cu(I) which again proceeds via a μ-peroxo complex $Cu_2O_2^{2+}$ [35], while an oxocupric species Cu_2O^{2+} is the active oxidant but has no oxygenative activity. Only the study of additional analogous systems can show if this coincidence is part of a generally valid rule.

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